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10/081,280	02/21/2002	Avi J. Ashkenazi	P1007R1C1	2465

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,280	ASHKENAZI, AVI J.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/13/05; 11/22/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-66* is/are pending in the application.

4a) Of the above claim(s) *56-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-55 and 64-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/21/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/11/05; 7/23/04; 11/26/03; 5/7/02,*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

DETAILED ACTION

1. Claims 46-66 are pending.

2. Applicant's election with traverse of Group 1, Claims 46-55 and 64-66 drawn to a method of blocking or inhibiting Apo-3 receptor using anti-Apo-3 antibody, filed 6/13/05, is acknowledged. The traversal is on the grounds that one of skill in the art would understand the specification to define the term "antibody" such that it encompasses compositions such as immunoadhesins. There is a commonality of function of the antibody (including immunoadesins) in Groups I and II as capable of blocking or inhibiting Apo-3 receptor induced apoptosis in mammalian cells expressing Apo-3 or Apo-3 receptor activation of NF-κB in these mammalian cells. There is no significant search burden in examining Groups I and II together. Both groups have been classified as belonging to the same class 424. In contrast to applicant's assertion that antibody discloses on page 17, lines 20-23 defines antibody encompasses immunoadhesins, the specification on page 17, lines 20-23 discloses the term "antibody" is used in the broadest sense and specifically covers single monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies) and antibody compositions with polyepitopic specificity. The specification does not define antibody is immunoadesin. As is well known in the art, immunoadhesin is a fusion protein comprising a polypeptide such as Apo-3 fused to Fc portion of an immunoglobulin. The functions of Fc fusion protein is to extend the half live of the Apo-3 polypeptide in plasma. The immunoadhesin such as Apo-3 receptor-Fc does not bind to the Apo-3 receptor comprising SEQ ID NO: 6. The Apo-3 immunoadhesin binds to Apo-3 ligand. On the other hand, antibody comprises an antigen binding site which binds to an Apo-3 receptor comprising SEQ ID NO: 6 also binds to the Apo-3 receptor. The two types of molecules therefore have different functions and binding specificity – binding to Apo-3 ligand versus binding to Apo-3 receptor, different modes of operation – extend half-lives versus protein-protein interactions. Thus, as was stated in the previous office action, they differ structurally and functionally. Reasons as to why the other groups are distinct are also provided in the previous office action. A product is distinct from a process of use if it has other uses. Methods are different if they use distinct product and have different method steps, goals, or outcome measures. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. With respect to the argument that the search and examination of all groups would not

entail a "serious burden", the separate classification of the different groups provides prima facie evidence of such a burden; see MPEP § 803. Furthermore, methods of using antibody versus immunoadhesin fusion protein represent different inventions and require different, non-contiguous searches, as evidenced by their different classification. They require separate searches of separate databases. A search of antibody databases does not reveal information about the fusion protein such as immunoadhesin. The search for methods of use is separate because it requires additional considerations as to the methodology itself. Thus to consider all of these groups would constitute an undue burden because each requires considerations that are separate from each of the others. Therefore, the requirement of Group 1 (Claims 46-55 and 64-66) and Group 2 (claims 56-63) is still deemed proper and is therefore made FINAL.

3. Claims 56-63 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 46-55 and 64-66, drawn to a method of blocking or inhibiting Apo-3 receptor using anti-Apo-3 antibody are being acted upon in this Office Action.

5. The reference 235 on PTO 1449, filed 5/7/02 has not been considered and crossed out because said reference is missing the volume and the date of publication.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 46-55 and 64-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO: 47, the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO: 6; the death domain of Apo-3 consisting of the amino residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody, **does not** reasonably provide enablement

for a method of blocking or inhibiting Apo-3 receptor comprising exposing any mammalian cells expressing any Apo-3 receptor to an effective amount of any anti-Apo-3 antibody, any antibody such as chimeric antibody, humanized antibody, monovalent antibody, labeled anti-Apo-3 antibody, wherein said antibody comprises any antigen binding site which binds to an Apo-3 polypeptide comprising SEQ ID NO: 6, or any immunogenic fragment thereof, or any Apo-3 receptor "comprises" amino acid residues 25 to 198 of SEQ ID NO: 6, or any Apo-3 receptor "comprises" amino acid residues 338 to 417 of SEQ ID NO: 6 or any soluble, truncated or secreted form of the Apo-3 receptor that blocks or inhibits Apo-3 receptor induced apoptosis in mammalian cells in vivo or Apo-3 receptor activation of NFκB in said mammalian cells as set forth in claims 46-55 and 64-66. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO: 47, the extracellular domain of Apo-3 consists the amino acid residues 25 to 198 of SEQ ID NO: 6, the death domain of Apo-3 consists the amino residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody. The specification further discloses the antibody *may be employed* to activate or stimulate apoptosis in cancer cells. Alternatively, antagonist antibodies *may be used* to block excessive apoptosis (for instance in neurodegenerative disease) or block potential autoimmune/inflammatory effects of Apo-3 resulting from NF-κB activation (page 62, lines 1-8, in particular).

However, the specification does not teach how to make any "antagonist antibody" having the properties of blocking excessive apoptosis in vivo for treating any neurological disease or blocking any Apo-3 receptor mediated activation of NF-κB activation in vivo for treating autoimmune/inflammatory effects associated with NF-κB activation in vivo. Further, the term "comprising" is open-end. It expands the amino acid residues 25 to 198 of SEQ ID NO: 6 or amino acid residues 338 to 417 of SEQ ID NO: 6 to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added and whether the resulting antibody still binds specifically to Apo-3 receptor comprising SEQ ID NO: 6, let alone the antibody may be used to inhibit apoptosis or NF-κB activation in vivo. Further, the specification is silent with respect to which particular neurodegenerative disease is associated with Apo-3 mediated apoptosis and which particular autoimmune disease is associated with Apo-3 mediated activation of NF-κB activation.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Kuby et al teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment may result in antibody specificity that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza et al teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Even if the antibody binds to the extracellular domain of the Apo-3 receptor comprising SEQ ID NO: 6, there is no evidence that the claimed antibody blocks Apo-3 receptor mediated apoptosis.

Coney et al teach antibody such as anti-Apo-1 antibody that binds to Apo-1 or Fas, a member of the NGFR1 supper family, induces apoptosis of cells expressing the APO-1 receptor, rather than inhibiting apoptosis (see abstract, in particular). Coney et al further teach that such antibody might only be therapeutically when the antibody can be targeted to cells expressing said receptor such as tumor cells.

Given the unlimited undisclosed antigen binding site to which the antibody binds, there is a lack of working example demonstrating that the anti Apo-3 that binds only to human Apo-3 comprising SEQ ID NO: 6 or any fragment thereof could inhibit apoptosis of any Apo-3 receptor expressed in any mammalian cells in vitro, let alone inhibit apoptosis in vivo for treatment of any neurological disease or treating any autoimmune/ inflammatory effects as a result of Apo-3 mediated NF-κB activation.

With regard to claims 52-53, there is insufficient guidance as how an anti-Apo-3 antibody labeled with a "detectable moiety" such as radioisotope, fluorescent compound or chemiluminescent compound could be used to "blocks or inhibits apoptosis" or "blocks or inhibits" Apo-3 receptor activation of NF-κB in mammalian cells.

With regard to claim 65, in addition to the problem of "comprising" mentioned above, the amino acid residues 338 to 417 of SEQ ID NO: 6 is a death domain of the Apo-3 receptor, which locates within the mammalian cell. However, antibody such as Apo-3 antibody is a large molecule that does not get inside the cell, especially cells in vivo. There is insufficient guidance as how the antibody such as Apo-3 antibody that binds to the death domain within the cell in vitro, much less the antibody binds to the death domain of any mammalian cell in vivo.

With regard to claim 66, there is insufficient guidance as how anti-Apo-3 antibody that binds to a "soluble, truncated or secreted form of Apo-3 receptor" is effective for blocking or inhibiting apoptosis or Apo-3 receptor activation of NF-κB activation in vivo since the cell is no longer expressed the Apo-3 receptor.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 46-55 and 64-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any Apo-3 antibody comprising any antigen binding site which binds to any immunogenic fragment of Apo-3 polypeptide comprising SEQ ID NO: 6, any Apo-3 receptor "comprises" amino acid residues 25 to 198 of SEQ ID NO: 6 and any Apo-3 receptor "comprises" amino acid residues 338-417 of SEQ ID NO: 6, any soluble, truncated or secreted from of any Apo-3 receptor for the claimed method of blocking or inhibiting Apo-3 receptor induced apoptosis or Apo-3 receptor activation of NFκB activation in vitro or in vivo.

The specification discloses only a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO: 47, the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO: 6, and the death domain of Apo-3 consisting of the amino residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody. The specification further discloses the antibody *may be employed* to activate or stimulate apoptosis in cancer cells. Alternatively, antagonist antibodies *may be used* to block excessive apoptosis (for instance in neurodegenerative disease) or block potential autoimmune/inflammatory effects of Apo-3 resulting from NF-κB activation (page 62, lines 1-8, in particular).

With the exception of the specific antibody mentioned above for a method of affinity purification of Apo-3 from recombinant cell culture or natural sources or a method of detection assay, there is insufficient written description about any and all Apo-3 antibody that has the property of blocking or inhibiting Apo-3 receptor induced apoptosis and/or Apo-3 receptor activation of NFκB activation for the claimed method. Further, the term "comprising" is open-end. It expands the amino acid residues 25 to 198 of SEQ ID NO: 6 or amino acid residues 338 to 417 of SEQ ID NO: 6 to include additional amino acids at either or both ends. There is inadequate written description about which amino acids to be added and whether the resulting antibody still binds specifically to Apo-3 receptor comprising SEQ ID NO: 6, in turn, may be useful for inhibiting apoptosis or NF-κB activation in mammalian cells in vitro or in vivo. There

is inadequate written description about any antibody that binds to soluble, truncated or secreted form of any Apo-3 receptor for the claimed method. Finally, there is inadequate written description about the "effective amount" of any anti-Apo-3 antibody for the claimed method.

The specification discloses only antibody that binds only to human Apo-3 receptor, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of anti-Apo-3 antibody for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 52-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "antibody is labeled with a detectable moiety" in claim 53 and "the antibody is labeled with a detectable moiety such as radioisotope, fluorescent compound or chemiluminescent compound" in claim 54 are ambiguous and indefinite because it is not clear to one of ordinary skill in the art how a labeled Apo-3 antibody could block or inhibit Apo-3 receptor induced apoptosis in mammalian cells or how a labeled antibody blocks or inhibits Apo-3 receptor activation of NFκB in mammalian cells. The specification discloses labeled Apo-3 antibody is used to detect Apo-3 in mammalian cells, NOT to block apoptosis or activation of NFκB in mammalian cells.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 46, 50-51, 54-55, 61 and 64-66 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,153,402 (with earliest filing date of March 12, 1996; PTO 892).

The '402 patent teaches a method of blocking apoptosis or inhibits Apo-3 receptor induced apoptosis comprising exposing mammalian cells expressing Apo-3 receptor to anti-Apo-3 antibody such as monoclonal antibody that binds to an Apo-3 receptor polypeptide comprising SEQ ID NO: 4 wherein SEQ ID NO: 4 is 100% identical to the claimed SEQ ID NO: 6 (see col. 22, lines 57-67, reference SEQ ID NO: 4, Figure 2, in particular). The '402 patent further teaches antibody includes Fab, which is a monovalent antibody (see col. 25, lines 35-42, in particular). The reference antagonist antibody is administered in vivo (see col. 27, lines 9-15, in particular). The term "comprises" is open-ended. It expands the 338 to 417 or 25 to 198 of SEQ ID NO: 6 to include the full length amino acid sequence to which the reference antibody binds. Claim 66 is included in this rejection because the '402 patent further teaches soluble, truncated or secreted from of the reference Apo-3 receptor (see col. 19, lines 62-67, col. 18, lines 41-51, in particular). Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,153,402 (with earliest filing date of March 12, 1996; PTO 892) in view of US Pat No. 6,180,370B, filed June 1995; PTO 892).

The teachings of the '402 patent have been discussed supra.

The invention in claim 47 differs from the teachings of the reference only in that the method wherein the antibody is a chimeric antibody.

The invention in claims 48-49 differs from the teachings of the reference only in that the method wherein the antibody is humanized antibody or human antibody.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular). The '370 patent further teaches that humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce humanized or chimeric antibody that is specific for the polypeptide of SEQ ID NO: 4 as taught by the '370 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce chimeric or humanized antibodies because the '370 patent teaches that chimeric antibody has proven somewhat successful since chimeric antibody can loose the affinity for the antigen; humanized immunoglobulin (antibody) binds with strong affinity to a predetermined antigen and remain nonimmunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). The '402 patent teaches antibody that binds to an Apo-

3 receptor polypeptide comprising SEQ ID NO: 4 is useful for blocking or inhibiting Apo-3 receptor mediated apoptosis or activation of NFκB (see col. 22, lines 57-67, reference SEQ ID NO: 4, Figure 2, col. 26, lines 63-67, in particular).

17. Claims 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,153,402 (with earliest filing date of March 12, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 340-355).

The teachings of the '402 patent have been discussed supra.

The invention in claim 52 differs from the teachings of the reference only in that the method wherein the antibody is labeled with a detectable moiety capable of directly or indirectly producing a signal.

The invention in claim 53 differs from the teachings of the reference only in that the method wherein the antibody is labeled with a detectable moiety capable of directly or indirectly producing a signal wherein the detectable moiety is a radioisotope, fluorescent compound or chemiluminescent compound.

Harlow *et al* teach a method of labeling any antibody directly or indirectly via biotin (see page 340, in particular) with various labels such as enzyme, fluorescent, radioisotope (See chapter 9, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity (See page 322, in particular). Harlow *et al* teach that the advantages of monoclonal antibody are their binding specificity, their homogeneity and their ability to be produced in unlimited quantities by hybridoma (See page 141, last full paragraph, in particular). The advantage of indirect labeling is that suitable secondary reagents labeled with flourochromes are available commercially and direct leveling may be the method of choice where such conjugates are not available or where a direct label is required specifically in simultaneously visualizing two antibodies of the same class or subclass (see page 353, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to labeled any antibody as taught by the '402 patent with the enzyme, fluorescent, radioisotope for detection assays as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to label any antibody because Harlow *et al* teach that the advantages of enzyme labeling are longer shelf life, and higher sensitivity (See page 322, in particular). The advantage of indirect labeling is that suitable secondary reagents labeled with flourochromes are available commercially and direct leveling may be the method of choice where such conjugates are not available or where a direct label is required specifically in simultaneously visualizing two antibodies of the same class or subclass (see page 353, in particular).

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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